A Register-Based Study of Diseases With an Autosomal Recessive Origin in Small Children in Denmark According to Maternal Country of Origin

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Abstract

Background: Compared with children born of Danish mothers, the mortality of children, born and living in Denmark, is significantly increased in those with a mother from Afghanistan, Iraq, Pakistan, Somalia, and Turkey. Consanguinity has been suggested to account for part of this disparity. Since information on consanguinity is lacking, this suggestion is difficult to test. With an indirect approach, we addressed this question by comparing the risk of diseases with autosomal recessive inheritance in children born in Denmark of Danish-born women and of women born in these five countries, respectively.

Methods: All children born in Denmark (1994–2010) were followed until 5 years of age or end-of-study period for the risk of hospitalisation with diseases of autosomal recessive aetiology, and therefore considered consanguinity-related. Diagnoses of autosomal recessive diseases were identified using two different methods: a literature review of consanguinity-associated diseases and a search in the Online Catalogue of Human Genes and Genetic Disorders. Risks were also calculated for diseases with known non-autosomal recessive aetiology (considered non-consanguinity-related). We estimated adjusted hazard ratios for the diseases in children of foreign-born women compared with children of Danish-born women.

Results: Compared with offspring of Danish-born women, the risk of a consanguinity-related disease was significantly increased in children of foreign-born women, although the absolute risk was low. The risk of non-consanguinity-related diseases did not differ between the groups compared.

Conclusions: The findings support the hypothesis that consanguinity accounts for some, however a minor part, of the disparity in child mortality among migrants in Denmark.

Keywords: *child health, minority groups, consanguinity, autosomal recessive, epidemiology.*

Considerable disparities in perinatal, infant, and under 5-year mortality (U5-mortality) have been observed between children born in Denmark in the period from 1973 to 2004 by mothers who migrated to Denmark from Afghanistan, Iraq, Pakistan, Somalia, and Turkey when compared with the majority of the population. The increased mortality was apparently not explained by differences in indicators of parental socio-economic position.[1,2] Higher childhood mortality rates among some ethnic minorities are well described in many Western countries, but the underlying causes behind these disparities are not fully established.[3–8] In an international meta-analysis, Bittles and Black found excess mortality among offspring of consanguine vs. non-consanguineous parents.[9] Offspring of consanguineous marriages are at greater risk of known autosomal recessive diseases, including congenital anomalies, for which recessive genes are presumed to play a part.[10–14] It is estimated that humans on average carry at least three to five of such potentially harmful recessive genes.[15] The risk of homozygosity in the offspring is clearly markedly increased when parents are related when compared with unrelated parents.[14]

Sheridan *et al.* recently reported significantly increased risks of congenital anomalies in children born to consanguineous parents using data from the large multiethnic Born in Bradford cohort.[10] They also reported no association between deprivation and

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congenital anomalies but an association between low maternal educational level and congenital anomalies, across all ethnic groups. In a Danish investigation, the excess mortality among children of Afghani, Iraqi, Pakistani, Somali, and Turkish women was especially due to congenital anomalies and 'other causes of death' (not including perinatal causes, external causes, and sudden death).[2]

No direct data on the prevalence of consanguineous marriages exist in Denmark. Based on data from Western countries, the frequency of related parents among ethnic Danish couples is expected to be below 1%.[16] Consanguineous marriages are estimated to occur in one fifth of the population residing in the Middle East and in estimated 10% worldwide.[9,14] Consanguinity has been estimated to be at 42% in Afghanistan, 33% in Iraq, 61% in Pakistan, and 20% in Turkey (no Somali data were available).[17] It is likely that the tradition of consanguine marriages remains after migration to Western countries. A possible explanation of the impaired health of children in some immigrant groups in Denmark could be consanguinity-related morbidity and mortality.

As an indirect approach to examine the role of consanguinity for the impaired child health in children of some immigrant groups in Denmark, this study compares the prevalence of selected autosomal recessive and therefore consanguinity-related morbidity in up to 5-year-old children born in Denmark to Danish-born and foreign-born women, respectively (women born in Afghanistan, Iraq, Pakistan, Somalia, and Turkey). Furthermore, we estimate the relative risk of such morbidity in children of foreign-born women compared with children of Danish-born women.

Methods

The study population included all liveborn children in Denmark during the period 1994–2010 of women who were born in Denmark, Afghanistan, Iraq, Pakistan, Somalia, and Turkey, with a total of 992 162 children. The population was identified using data from the Danish Civil Registration System, where information on country of origin is registered on all inhabitants in Denmark.[18] The population was individually linked with information from the Danish National Patient Register, where all discharge diagnoses from somatic hospital inpatient and outpatient contacts are registered.[19] The population was followed from birth up to the age of 5 years for occurrence of one or more of the diagnoses in the diagnose groups described below.

We used two different approaches in order to identify diseases of autosomal recessive origin. First, we conducted a literature review based on the following search combination in the database PubMed: 'Consanguinity' was marked as (MeSH major topic), while 'human', 'abnormality, congenital' and 'inborn errors of metabolism' were marked as (MeSH term). The search was restricted to papers in the English language. Based on a review of these papers, we created a list of autosomal recessive diseases and conditions (available from the authors on request), only using diseases described in the Online Catalogue of Human Genes and Genetic Disorders (OMIM) database to have at least one autosomal recessive genotype.[20] We categorised the diseases into five groups: 'congenital anomalies', 'inborn errors of metabolism', 'severe and profound intellectual disability', 'diseases of the nervous system', and 'diseases of the sensory organs', including the International Classification of Diseases-10 (ICD-10) codes correspondent to the disease name.

Second, all autosomal recessive diseases with a described molecular basis were sought and identified by the search term 'autosomal recessive' using the advanced search function at the www.omim.org web site. The group of diseases identified using this method was labelled 'overall autosomal recessive diseases'.

In general, many of the diseases were rare and do not have unique ICD-10 codes. We used a method described by Goh *et al.*[21] to transform the OMIM disease names into ICD-9 codes, which subsequently were translated into ICD-10 codes using an ICD-10 code converter.[22]

To serve as negative controls, i.e. conditions that definitely not are of autosomal recessive aetiology, we defined two groups of diseases: 'Down's syndrome' and 'genetic diseases without autosomal recessive aetiology'. The ICD-10 codes included in each of the eight disease groups are presented in Table 1.

We described the prevalence proportions of the eight disease groups in children of Danish women and children of foreign-born women. If a child had more than one diagnosis within one of the disease groups during the first 5 years of life, only the first diagnosis counted as a case. A specific child was allowed to be a case in all groups of diagnoses.

Table 1. Disease groups in the study and the corresponding International Classification of Diseases-10 (ICD-10) codes

Disease group	ICD-10 codes
Congenital anomalies; described to be part of an autosomal recessive disorder	Q02, Q04.3F, Q04.8, Q11.2, Q13.2, Q20-24, Q43.1, Q61.1, Q61.5, Q75.0, Q75.1, Q75.2, Q75.3, Q75.8, Q75.9, Q76.2, Q76.4, Q76.5, Q76.6, Q77.3, Q77.6, Q78.0, Q78.1, Q78.2, Q78.8, Q78.9, Q79.6, Q79.8, Q79.9, Q80.4, Q80.9, Q82.4, Q82.8, Q87.1E, Q89.3, Q89.8
Inborn errors of metabolism; described to be part of an autosomal recessive disorder	E70.0, E70.8, E71.0, E72.0, E72.1, E72.2, E72.8, E72.9, E73.9, E74.0, E74.1, E74.2, E74.8, E74.9, E75.2E, E75.4, E76.3, E78.2, E78.8, E83.0B, E84, E88.8
Severe and profound mental retardation	F72-73, F79.9
Diseases of the sensory organs; described to be part of an autosomal recessive disorder	H35.5F, H53.5, H91.9
Diseases of the nervous system; described to be part of an autosomal recessive disorder	G12.1, G12.8, G12.9, G60.0, G72.8, G90.9, G91.1
Overall autosomal recessive diseases	D70, D71, D72.0, D72.1, D72.8, D72.9, D80.0, D80.2, D80.3, D80.4, D80.5, D80.8, D81.4, D81.9, D83.0, D83.1, D83.8, D84.9, D89.8, D89.9
	E25.9, E27.4, E72.0, E73.9, E74.0, E74.1, E74.2, E74.8, E74.9, E75.4, E75.6, E78.0, E78.1, E78.2, E78.3, E78.4, E78.6, E78.8, E78.9, E88.1
	F79.9
	G11.9, G12.1, G12.8, G12.9, G20, G58.9, G60.0C, G71.0F, G72.9, G91.1
	H26.9, H35.5E, H52.1, H53.6, H91.9
	I42.8, I49.5, I82.9
	K00.5
	L53.8, L64.8, L85.1
	M35.9
	N04.9, N46
	Q02, Q74.8, Q75.0, Q75.1, Q75.2, Q75.3, Q75.8, Q75.9, Q76.1, Q76.2, Q76.4, Q76.5, Q76.6, Q77.3, Q77.6, Q78.0, Q78.1, Q78.2, Q78.8, Q78.9, Q79.6, Q79.8, Q79.9, Q80.9, Q82.4, Q82.8, Q89.8
Genetic diseases without autosomal recessive aetiology	Q77.4, Q82.1, Q85.0, Q87.2D, Q90, Q93.5C, Q96, Q98.0, Q98.1, Q98.4, Q99.2
	D66, D67, D82.1
	F84.2
	G71.0H
Down's syndrome	Q90

The hazard ratio (HR) with 95% confidence intervals [95% CI] of being diagnosed in a disease group was estimated for children of foreign-born women relatively to children of Danish-born women using Cox regression models. Age was the underlying time-scale, and the children were followed from birth to first diagnosis in each of the disease groups, emigration, death, 5-year birthday, or December 2010, whichever came first. We made three steps of adjustment: model one was adjusted for maternal age (5-year groups) and year of birth. Model two was furthermore adjusted for paternal age (5-year groups), parity (0, 1–2, 3, or more), maternal smoking during pregnancy (no, yes), and maternal pre-pregnant chronic disease, which included diabetes, epilepsy, inflammatory bowel disease, and autoimmune disease (no, yes). In the third model, we further adjusted for socioeconomic indicators: maternal educational level in the year of birth. Only children with complete data on all covariates were included in the regression analyses.

Finally, as subanalyses, we repeated all analyses above for each of the five maternal countries of origin separately. All linkages and storage of data were done by Statistics Denmark and handled according to Danish legislation. Approval from the Danish Data Protection Agency was obtained prior to commencement of the study.

Results

Women born in Denmark, Afghanistan, Iraq, Pakistan, Turkey, and Somalia gave birth to a total of 992 162 liveborn children during the period 1994–2010. Of these, 944 206 children were born to Danish-born women, 2744 to Afghani-born women, 8433 to Iraqi-born women, 7756 to Pakistani-born women, 9916 to

Table 2. Distribution of selected characteristics of study population according to maternal country of origin (percentages unless otherwise indicated): liveborn children in Denmark, 1994–2010

	Danish-born mothers (n = 944 206)	Foreign-born mothers[a] (n = 47 956)
Maternal age at birth (years)	29.7 (4.7)	28.0 (5.5)
<25	13.1	28.98
25–29	35.44	33.86
30–34	35.6	23.81
35–39	13.73	10.79
40+	2.13	2.56
Paternal age at birth (years)	32.1 (5.5)	32.2 (6.9)
<25	6.15	11.97
25–29	25.77	24.53
30–34	36.93	26.41
35–39	20.39	18.72
40+	8.86	13.75
Missing	1.9	4.63
Maternal parity at birth		
1	43.76	30.44
2–3	52.16	48.76
4+	4.08	20.8
Maternal educational (years)		
<10	17.3	44.68
10–12	41.41	29.71
> 12	40.94	11.28
Missing	0.34	14.33
Paternal income quintile		
First (lowest)	16.68	48.54
Second	19.07	23.14
Third	20.46	9.3
Fourth	20.54	7.09
Fifth (highest)	20.32	4.6
Missing	2.93	7.33
Maternal income quintile		
First (lowest)	16.86	41.5
Second	19.48	27.31
Third	20.74	15.11
Fourth	21.36	8.48
Fifth (highest)	21.48	4.59
Missing	0.08	3.02
Maternal smoking during pregnancy		
Yes	12.77	11.08
No	83.58	84.34
Missing	3.64	4.59
Maternal pre-pregnant medical conditions		
Yes	2.51	1.85
No	97.49	98.15

[a]Afghanistan, Iraq, Pakistan, Somalia, or Turkey.

Somali-born women, and 19 107 to Turkish-born women. Tabulating the baseline characteristics of the study population (Table 2), children of foreign-born women were seen to have younger mothers and a higher birth order, and to have more educationally and economically disadvantaged parents, while the groups did not differ with respect to maternal smoking and history of chronic disease. When excluding those with missing information on one or more covariates, 935 093 were included in the proportional hazards regression analyses.

The literature search in PubMed resulted in 297 papers. The abstracts were screened for relevance, and 150 papers were found to describe one or more diseases suspected to be of autosomal recessive origin. A list of 79 autosomal recessive diseases was created. During the conversion from OMIM code to ICD-10 code, 15 diseases were excluded because of lack of disease ID from Goh *et al.*,[21] and three diagnoses were excluded due to lack or very imprecise conversion from ICD-9 to ICD-10 code. The remaining diagnoses were split into the five disease groups described in the Methods section.

The advanced search for autosomal recessive diseases in the OMIM database resulted in 76 diseases (192 genotypes). Two diseases were excluded due to autosomal dominant aetiology, 19 due to lack of a disease ID from Goh *et al.*,[21] and 4 due to lack of or very imprecise conversion from ICD-9 to ICD-10 code. The remaining diagnoses were grouped as 'overall autosomal recessive diseases'.

Tables 3–5 show the absolute number and prevalence proportion of children diagnosed in the disease groups – for children of foreign-born women and children of Danish-born women. The relative risks, estimated as unadjusted and adjusted HRs using children of Danish-born women as the reference, are also shown. Table 3 refers to diseases found in the PubMed review, Table 4 refers to diseases found in the OMIM-search, and Table 5 refers to diseases with known non-autosomal recessive aetiology.

The children of foreign-born women had a higher risk of being diagnosed in all the disease groups defined on the basis of the 'literature review' (considered consanguinity related), expressed as prevalence proportions. The unadjusted HRs were also significantly increased for all disease groups, but after all three steps of adjustment the risks only remained statistically significantly increased in the groups of 'inborn errors of metabolism', 'severe and profound intellectual disability', and a 'diseases of sensory organs' (HR 2.08 [95% CI 1.58, 2.74], 2.67 [95% CI 2.02, 3.51], and 1.57 [95% CI 1.24, 1.98], respectively) (Table 3).

Table 3. Number of cases, prevalence proportions, and hazard ratio for disease according to maternal country of birth

Disease group	Total cases	Prevalence proportion per 10 000	n cases[a]	Unadjusted HR [95% CI]	Adjusted HR[b] [95% CI]	Adjusted HR[c] [95% CI]	Adjusted HR[d] [95% CI]
Congenital anomalies related to autosomal recessive disorders							
Danish-born mothers	12 936	129	12 010	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	769	151	673	1.18 [1.09, 1.28]	1.16 [1.08, 1.26]	1.17 [1.08, 1.26]	1.06 [0.98, 1.16]
Inborn errors of metabolism related to autosomal recessive disorders							
Danish-born mothers	616	7	581	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	80	15	73	2.67 [2.09, 3.40]	2.40 [1.87, 3.07]	2.37 [1.85, 3.03]	2.08 [1.58, 2.74]
Severe and profound intellectual disability							
Danish-born mothers	601	8	542	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	95	24	78	3.09 [2.44, 3.92]	2.93 [2.30, 3.73]	2.88 [2.26, 3.67]	2.67 [2.03, 3.51]
Diseases of the sensory organs related to autosomal recessive disorders							
Danish-born mothers	1175	13	1093	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	107	23	94	1.84 [1.49, 2.27]	1.82 [1.47, 2.25]	1.83 [1.48, 2.26]	1.57 [1.24, 1.98]
Diseases of the nervous system							
Danish-born mothers	311	3	283	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	27	6	22	1.65 [1.07, 2.55]	1.54 [0.99, 2.38]	1.53 [0.99, 2.38]	1.30 [0.81, 2.11]

The unadjusted and adjusted hazard ratios (HR) were derived using children born of mothers born in Denmark as reference (for disease groups identified in the PubMed review).
[a]Complete cases in Cox proportional hazards regression.
[b]Adjusted for maternal age and period.
[c]Adjusted for maternal age, period, paternal age, parity, smoking, maternal pre-pregnant chronic medical condition.
[d]Adjusted for maternal age, period, paternal age, parity, smoking, mother's educational level, maternal income quintile, maternal pre-pregnant chronic medical condition.
[e]Afghanistan, Iraq, Pakistan, Somalia, or Turkey.

Children of foreign-born mothers also had a significantly greater risk of being diagnosed with a disease in the group found in the OMIM search, denoted 'overall autosomal recessive diseases' (adjusted HR 1.58 [95% CI 1.43, 1.75] after three steps of adjustment) (Table 4).

For genetic diseases known to have a non-autosomal recessive aetiology, we found no statistically significant differences in prevalence between the children born of Danish-born women and foreign-born women (Table 5).

Within the group of children of foreign-born women, children of women with Afghani and Iraqi origin had no significant increased risk of the disease groups assumed to be of autosomal recessive origin

Table 4. Number of cases, prevalence proportions, and hazard ratio for disease according to maternal country of birth

Disease group	Total cases	Prevalence proportion per 10 000	n cases[a]	Unadjusted HR [95% CI]	Adjusted HR[b] [95% CI]	Adjusted HR[c] [95% CI]	Adjusted HR[d] [95% CI]
Overall autosomal recessive diseases							
Danish-born mothers	6602	70	6116	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	592	123	515	1.79 [1.64, 1.96]	1.74 [1.59, 1.91]	1.74 [1.59, 1.91]	1.58 [1.43, 1.75]

The unadjusted and adjusted hazard ratios (HR) were derived using children born of mothers born in Denmark as reference (for diseases identified in the OMIM search).
[a]Complete cases in cox regression.
[b]Adjusted for maternal age and period.
[c]Adjusted for maternal age, period, paternal age, parity, smoking, maternal pre-pregnant chronic medical condition.
[d]Adjusted for maternal age, period, paternal age, parity, smoking, mothers educational level, maternal income quintile, maternal pre-pregnant chronic medical condition.
[e]Afghanistan, Iraq, Pakistan, Somalia, or Turkey.

Table 5. Number of cases, prevalence proportions, and hazards ratio for disease according to maternal country of birth

Disease group	Total cases	Prevalence proportion per 10 000	n cases[a]	Unadjusted HR [95% CI]	Adjusted HR[b] [95% CI]	Adjusted HR[c] [95% CI]	Adjusted HR[d] [95% CI]
Genetic diseases without autosomal recessive aetiology							
Danish-born mothers	1361	15	1260	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	83	18	73	1.22 [0.97, 1.55]	1.26 [0.99, 1.59]	1.22 [0.96, 1.55]	1.05 [0.81, 1.36]
Down's syndrome							
Danish-born mothers	730	9	677	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born mothers[e]	46	9	38	1.18 [0.85, 1.63]	1.29 [0.93, 1.79]	1.28 [0.92, 1.78]	1.23 [0.86, 1.77]

The unadjusted and adjusted hazard ratios (HR) were derived using children born of mothers born in Denmark as reference (for genetic diseases with known non-autosomal recessive aetiology).
[a]Complete cases in Cox regression.
[b]Adjusted for maternal age and period.
[c]Adjusted for maternal age, period, paternal age, parity, smoking, maternal pre-pregnant chronic medical condition.
[d]Adjusted for maternal age, period, paternal age, parity, smoking, mothers educational level, maternal income quintile, maternal pre-pregnant chronic medical condition.
[e]Afghanistan, Iraq, Pakistan, Somalia, or Turkey.

found in the literature review and the OMIM search (except an increased risk for children of Afghani-born women in the group 'overall autosomal recessive diseases' (adjusted HR 1.55 [95% CI 1.09, 2.22] after three steps of adjustment), while the risks were substantially and significantly elevated in the offspring of women from Turkey and Pakistan in the following disease groups: 'congenital anomalies' (only children of Pakistani women), 'inborn errors of metabolism', 'severe and profound intellectual disability', 'diseases of the sensory organs', and 'overall autosomal recessive diseases'. Children of Somali-born women showed a significantly increased risk of being diagnosed within the group 'inborn errors of metabolism', but no significantly elevated risk was found in the other disease groups considered consanguinity-related.

We found an increased adjusted risk of 'Down's syndrome' and 'genetic diseases without autosomal recessive aetiology' in children of Somali-born women, but – as expected – not any statistically significant increased risk for these diseases in offspring of the women who had migrated to Denmark from other countries.

Comment

The results of this study show significantly higher risks of being diagnosed with a condition that may be due to an autosomal recessive disorder within the groups of 'inborn errors of metabolism', 'severe and

profound intellectual disability', 'diseases of the sensory organs', and 'overall autosomal recessive diseases' before the age of 5 years in children born of foreign-born women when compared with children born of Danish-born women. The same group of children born of foreign-born mothers showed no statistically significant elevated risks of being diagnosed with 'Down's syndrome' and 'genetic diseases without autosomal recessive aetiology' before the age of 5 years. Those are diseases without autosomal recessive aetiology and therefore not consanguinity-related.

Examining the group of children born of foreign-born women in five groups according to mother's country of birth revealed differences in risks of consanguinity-related morbidity. Children born of Pakistani and Turkish women had the highest risks of being diagnosed in the groups of consanguinity-related diseases. No elevated risk (except for an increased risk in the disease group 'overall autosomal recessive diseases' for children of Afghani-born women) of consanguinity-related diseases was found regarding children of Afghani-born and Iraqi-born women living in Denmark. Children of Somali-born women had increased risks of being diagnosed with 'inborn errors of metabolism', but no increased risk in any of the other disease groups considered consanguinity-related. They also showed an increased risk of 'Down's syndrome' and 'genetic diseases without autosomal recessive aetiology'. These risks

remained statistically significant after all steps of adjustment, including age of the mother. This indicates that the aetiology behind the increased morbidity and mortality in children of Somali-born women is very complex and that consanguinity is unlikely to be the main underlying explanation. A recent Swedish study indicated that pregnant Somali-born women living in Sweden made less visits to antenatal care, and booked their first visit later than Swedish-born women.[23] This could be one of the explanations to the increased morbidity and mortality in children of Somali-born women.

We used two different approaches to identify autosomal recessive diseases. We made a review in PubMed resulting in 79 autosomal recessive diseases and a text search in the OMIM database for autosomal recessive diseases resulting in 76 diseases. Only a small part of the diseases found in the two different approaches overlapped. This indicated that neither of the two approaches succeeded in identifying all autosomal recessive diseases. Therefore, we are not able to estimate the exact extent of children diagnosed with autosomal recessive diseases in Denmark during the study period.

A recent study of congenital anomalies in the Born in Bradford cohort found consanguinity to be a major risk factor for congenital anomalies in children.[10] Ethnic differences in prevalence of congenital anomalies disappeared when children born of consanguineous couples were excluded. The same tendency was seen in a study from Birmingham.[24] Stoltenberg *et al.* found that adjustment for consanguinity in addition to period and place of birth almost erased the higher risk of birth defects found in children of Pakistani parents living in Norway compared with the Norwegian population.[12] In this study, we explored different groups of autosomal recessive and therefore consanguinity-related diseases, and found that the risk of being diagnosed with these diseases was significantly elevated in children of foreign-born women. We found no significant elevated risk of congenital anomalies after all three steps of adjustment. This could be due to the converting process from diagnosis to ICD-10 code. The highest risk was found in the group of 'severe and profound intellectual disability'. The results of this report support the hypothesis that consanguinity may play a role in the disparities of health in Danish-born children of women with different countries of origin.[2]

In line with an earlier report from Denmark, we found that the group of children of foreign-born women had significantly higher risks of being diagnosed in the group of 'severe and profound intellectual disability' compared with children of Danish-born women.[25] This disease group is aetiologically and genetically heterogeneous but was included in the analyses because several of the autosomal recessive syndromes included in the groups of diagnoses have intellectual disability as one of the core symptoms. An increasing number of autosomal recessive genes involved in non-syndromic intellectual disability have been identified in recent years.[26] Also, other studies have found elevated risks of severe intellectual disability in offspring of consanguine parents.[13,27] We consider it likely that consanguinity contributed to the higher risk of intellectual disability in children of foreign-born women, but numbers are small, and more detailed studies of diagnoses are required.

Other studies have been carried out on autosomal recessive diseases in ethnic groups living in Western countries. Kleijer *et al.* showed a significant higher incidence of three autosomal recessive DNA repair deficiency disorders among immigrant populations with high rates of consanguinity in northern Europe,[28] and Bajaj *et al.* found a prevalence of deafness twice as high in British Bangladeshi children than in the UK population and assigned a part of the explanation to consanguinity.[29] Both of these studies are in accordance with our findings.

We used the Danish nationwide registry data in the analysis, which gave us an unselected sample of the Danish population. This is one of the primary strengths of this study.

We included liveborn children only, and thereby excluded the potential cases among fetuses and stillbirths. These cases are not collected in the registries used in this study. A recent Danish study indicated that a higher percentage of women with non-Scandinavian country of origin would decline a first trimester risk assessment for Down's syndrome.[30] In general, utilisation of the health care system, including antenatal diagnostics and termination of pregnancy due to fetal abnormality, may vary between women of different countries of origin, and this may also contribute to the health disparities observed in Denmark.

Data about relatedness of parents are not routinely collected in Danish registries, and our study did not include direct information on consanguinity.

Therefore, we have looked at several groups of diseases assumed to have autosomal recessive inheritance to indirectly assess the significance of consanguinity to morbidity and mortality in children in Denmark. One assumption was that the groups of diseases represented autosomal recessive diseases. ICD codes refer to a mixture of aetiology and phenotype, and it was therefore impossible to extract only autosomal recessive diagnoses. This may have resulted in misclassification, most likely in the direction of underestimated HR. However, the groups of diseases are based on a review of recognised autosomal recessive diseases traced through the PubMed database and OMIM, and are likely to include a large part of the consanguinity-related cases.[31]

Autosomal recessive diseases, especially very rare diseases, are much more prevalent in consanguineous populations, but we cannot ascribe all cases of autosomal recessive diseases to consanguinity. Nevertheless, consanguinity increases the risk of autosomal recessive diseases in the offspring, and therefore when incidence of autosomal recessive diseases is significantly elevated in specific populations consanguinity is very likely to be the explanation.

In Norway, any pre-marriage familial relation between parents is registered in the Medical Birth Registry. Considerable focus has been on consanguinity and related health consequences. In 2007 Surén and Stoltenberg[32] and in 2009 Grjibovski *et al*.[33] found a substantial decrease in the amount of consanguine parents in the Pakistani minority in Norway. Zlotogora and Shalev investigated consanguinity in a village in Israel with high rates of consanguineous marriages.[34] They found a significant decline in first-cousin marriages (patrilineal first-cousin marriages) over time and an equivalent increase in marriages between more distantly related individuals. They ascribed a part of these changes to education programmes, including media campaigns particularly emphasising the medical risks of first-cousin marriages. The review by Hamamy[14] concerning guidelines for preconception counselling related to consanguinity suggests ensuring of access to preconception and premarital counselling services to address the health burden of consanguinity.

In conclusion, the results of this report support the theory that consanguinity contributes to the higher infant mortality and morbidity found in children of women born in Pakistan and Turkey living in Denmark. However, the very low incidence of the diseases studied indicates that consanguinity probably only explains a minor part of the child health disparity in Denmark. While we acknowledge that pre-marriage familial relations between parents may have many advantages, we do recommend increased information about the biological risks to relevant communities, as well as counselling on the increasing possibilities of genetic testing to identify carriers and pregnancies at risk.

Acknowledgements

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